II. REMARKS

Preliminary Remarks

Amendment of the Specification

The specification is amended to describe the deposited material, identify the name and address of the depository, and the date and designation numbers of the deposits, pursuant to 37 C.F.R. § 1.809(d).

Amendment of the Claims

Claims 34-36, 39, 41, 42, and 49 are amended, and claims 37, 38, 40 and 50 are canceled.

Claims 34-36 are amended by removing references to pre-malignant lesions, and claim 37 is canceled, in accord with the election.

Claim 34 is further amended to specify a detectable antibody that recognizes and binds to activated matriptase, as described in the specification, for example, in paragraph 2. This amendment incorporates the subject matter of claim 38, which is canceled.

Claim 49 is similarly amended to specify that the detectable agent is an antibody, incorporating the subject matter of claim 50, which is canceled.

Dependencies of claims 39, 41 and 42 are amended in accordance with the foregoing.

Patentability Remarks

35 U.S.C. §112, first paragraph/enablement

Claims 34-36, 38-44, and 48-49 are rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly fails to enable one of skill in the relevant art to practice the claimed method. *See* part 5 of the official action (pages 2-11).

The applicants submit that the teachings of the specification, in combination with the knowledge of one of skill in the art of detecting and treating malignant cancer, provide information and direction sufficient to enable one of skill in the art at the time of filing to successfully practice the claimed method having to perform undue experimentation.

The examiner acknowledges that the specification expressly describes the invention as relating to treatment of cancer by the inhibition of matriptase, but points to portions of the specification where the inventors indicate that further research is needed to elucidate molecular interactions and mechanisms by which matriptase promotes tumor growth and invasion as evidence of lack of enablement. For example, in paragraph 71 the inventors reported that some but not all invasive carcinoma tumor specimens examined had a relatively high matriptase/HAI-1 ratio, and that further studies of the correlation between the matriptase/HAI-1 ratio and the stage or pathology of tumors and patients' response to chemotherapy and overall prognosis are in progress; and in paragraph 98 the inventors call for further study of the molecular mechanisms by which matriptase effects degradation of extracellular matrix (ECM) and epithelial motility. The examiner further alleges that the language the inventors use in summarizing the scientific data disclosed in the specification, *e.g.*, the use of the word "may," suggests speculation and uncertainty about the role of matriptase in cancer etiology.

The applicants submit that the specification provides scientific data that demonstrates that matriptase is consistently and efficiently expressed by at least human breast, ovarian, uterine, and colon carcinoma tumors (*see* paragraphs 55-60), and data from analysis of the regulation of matriptase expression in breast cancer samples that indicates that matriptase expression by malignant cancer cells is constitutive, whereas matriptase expression in normal tissue is sensitive to regulatory factors in serum (*see* paragraph 95). At the time of filing, matriptase was known to recognize and activate the plasmin/urokinase type plasminogen activator system (uPA) and hepatocyte growth factor/scattering factor (HGF/SF), which are tumor-promoting factors produced by stromal cell components of tumor tissues. uPA is a protease that degrades ECM and promotes cancer invasiveness and metastasis; and HGF/SF is a growth and motility factor that promotes ECM degradation, cancer invasiveness, tumor growth, and angiogenesis (*e.g.*, see paragraphs 4 and 95). The inventors are medical scientists, and in describing the data that supports the invention, they have conscientiously indicated that further experimentation is needed across the range of subject matter that was investigated in support of the invention. The application clearly and unequivocally teaches that the presence of a malignancy can be diagnosed by assaying a biological sample to detect activated matriptase, and that a malignant cancer associated with activated matriptase can be treated by administering an agent that binds to active matriptase and blocks its activity. Upon considering the experimental results disclosed in

the specification as a whole, one of skill in the art would reasonably regard the claimed invention as being clearly supported and enabled by the applicants' disclosure. Scientific articles published after the present application was filed corroborate the teachings by the present specification that dysregulation of matriptase expression promotes malignant transformation (*see* List et al., 2005), and that matriptase promotes invasiveness and growth of malignant tumors through activation of uPA and HGF/SF (*see* Suzuki et al., 2004; and Kang et al., 2003). Moreover, Suzuki et al. (2004) demonstrates that inhibition of the expression of matriptase *in vivo* in nude mice inhibits the growth of tumors in the mice grown from transplanted uPA-stimulated ovarian cancer cells (*see* page 14906). Copies of List et al. (2005), Suzuki et al. (2004), and Kang et al. (2003) are attached.

The examiner further alleges that the specification does not enable one of skill in the art to practice the claimed invention, because the treatment of cancer is known to be unpredictable. Gura (1997) is cited as teaching that only a small percentage of drugs shown to have anti-tumor activity are useful for chemotherapy, and Jain (1994) is cited as teaching that administration of anti-tumor drugs to the interior of a tumor is problematic, because differential pressures favor delivery of anti-cancer molecules to peripheral tissues of a solid tumor but impede their delivery into the tumor interior (*see* page 63). Curti (1993) is cited for its teaching that solid tumors resist destruction by anti-cancer agents and its discussion of various mechanisms by which cancer cells overcome anti-cancer treatments (*e.g.*, production of proteins that confer drug resistance, and evasion of immune surveillance). Hartwell (1997) is cited as teaching that in order to be effective, an anti-cancer agent must selectively kill tumor cells. White et al. (2001) is cited as teaching that effective targeting of a tumor antigen by an antibody requires that the targeted antigen be present on all or nearly all of the malignant cells, and that shedding of the target antigen can reduce efficacy due to competition for the antibody by the shed antigen. The examiner further alleges that the invention is unpredictable because (i) matriptase activity may be inhibited by HAI-1 *in vivo*, (ii) the agents used to detect and/or inhibit tumor-associated matriptase may be inhibited by binding to matriptase produced by non-cancerous, normal cells such as granulocytes and smooth muscle cells (*see* paragraphs 34-35), and (iii) it is unclear whether matriptase is present on all or nearly all of the malignant cells, so as to allow effective targeting of the matriptase-producing cells.

The applicants agree that the treatment of cancer is unpredictable. It is well-known by persons skilled in the art of cancer treatment that individual cancers belonging to any specific cancer classification or type (*e.g.*, melanoma, colon carcinoma, neuroblastoma) have unique molecular and cellular characteristics and that the response of a cancer to a particular therapeutic agent is typically unpredictable. Therefore, the efficacy of a given anti-cancer agent in treating a cancer of a specific type is frequently described as a probability that the agent will have anti-cancer activity against the type of cancer in question (*i.e.*, the percentage of patients expected to respond). For example, colon cancer is relatively resistant to anti-cancer agents, and the probability that a patient with colon cancer will respond to an anti-cancer agent is usually considered to be relatively low; whereas the probability that a patient with a different type of cancer will respond to the same agent drug might be significantly greater. The applicants submit that despite the unpredictability inherent in cancer therapy, one of skill in the art would be able to practice the claimed invention successfully without having to perform undue experimentation.

Gura (1997) describes efforts to identify cancer cell lines, tumor cell culture methods, and genetic cancer cell markers, for use in screening anti-cancer drugs to provide improved predictions of anti-cancer efficacy than are obtained using murine xenograft model systems. The references in Gura (1997) to the small percentage of anti-tumor drugs tested that are found to be useful for chemotherapy pertain to the relatively small number of tested compounds that have been approved by the U.S. Food and Drug Administration (F.D.A.). In order to win approval by the F.D.A for use by the public, an anti-cancer drug must satisfy criteria that are in many ways more stringent than those required to determine patentability under 35 U.S.C. 112, first paragraph. For example, approval by the F.D.A. is determined in part by the number and type of side effects caused by the drug relative to the degree of therapeutic benefit conferred, whereas in determining compliance with 35 U.S.C. 112, first paragraph, of an application claiming an anti-cancer agent or therapeutic method, the focus is properly upon the ability of the agent or method to inhibit tumor growth and malignancy in a subject. Accordingly, it is not uncommon for an anti-tumor agent that is described in a patent specification and claims that comply with the requirements of 35 U.S.C. 112, first paragraph, to fail to win approval by the F.D.A.

A major concern of the Gura (1997) reference is that compounds with significant anti-cancer activity are frequently undetected by murine xenograft model system, because the cancer

cell line used in the xenograft is non-responsive, while other cancers of the same type that are not tested may sensitive to the agent being tested. Failure to detect inhibition of tumor growth in a murine xenograft system is not an issue for the claimed method. As noted above, inhibition of matriptase in a nude mouse transplanted with ovarian cancer cells inhibits the ovarian tumor growth in the mice (*see* Suzuki et al., 2004). Galkin et al. (2004) similarly demonstrated that administration of a small molecule matriptase inhibitor to mice with prostate tumor xenografts inhibits prostate tumor growth in the mice; and Foltz et al. (2005) have shown that administration of an inhibitory anti-matriptase antibody to SCID mice with B cell lymphoma tumor xenografts inhibits the growth of the lymphoma tumors in the treated mice (abstracts attached). The specification teaches that malignant cancer associated with expression of matriptase by the cancer cells can be treated by administering an agent that blocks the activity of active matriptase. Agents that block the activity of active matriptase were described prior to the filing of the present application (*e.g.*, see Long et al. (2001) and Enyedy et al. (2001), abstracts attached). Matriptase is a serine protease, and persons of skill in the art at the time of filing would have been familiar with protocols for preparing and screening agents to identify an agent that effectively inhibits a serine protease of interest, and would reasonably have expected that additional matriptase inhibitors suitable for use in the claimed invention could be obtained by such methods without undue experimentation. Indeed, various additional inhibitors of matriptase have been described in articles published after the present application was filed; *e.g.*, Yamasaki et al. (2003) describe short (3-residue) peptide-based inhibitors of matriptase; Stoop et al. (2003) describe longer peptides (about 20 residues) that inhibit matriptase; Galkin et al. (2004) describe a small-molecule inhibitor of matriptase; Forbs et al. (2005) describe two 3-amidinophenylalanine-type inhibitors of matriptase; Foltz et al. (2005) describe an antibody that binds and inhibits active matriptase; and Desilets et al. (2006) describe variants of the serine protease inhibitor eglin c that inhibit matriptase (abstracts attached). The published results described above are strongly corroborative of the teachings of the present application and of the ability of one of skill in the art to practice the claimed method successfully.

The therapeutic approaches described by Jain (1994), Curti (1993), Hartwell (1997), and White et al. (2001), involve contacting tumor cells with a cytotoxic agent, *e.g.*, a chemotherapeutic DNA-damaging agent or an radiolabeled antibody. Such cytotoxic antibodies

must bind to antigens on the surfaces of the targeted tumor cells in order for the tumor cells to be killed by the chemotherapeutic or radioactive cytotoxic agent that is attached to the antibody. Delivery of therapeutically effective amounts of such cytotoxic antibodies to tumor cells in the interior of a tumormay be prevented by physical barriers, as discussed in the cited references (*e.g.*, see Jain, p. 30). Unlike the methods for treating cancer discussed in the cited references, which involve administering cytotoxic agents that bind to the tumor cells and kill them, the claimed method comprises administering a therapeutic amount of a matriptase-inhibiting agent that inhibits active matriptase enzyme at the site of a malignant tumor. Tumor growth and invasion into surrounding tissue involves direct contact between the tumor and the surrounding normal tissues, and is promoted by the activities of matriptase in the peripheral region where tumor cells contact the surrounding normal tissues. Therapeutic benefit therefore results from inhibiting matriptase enzyme activity in the peripheral portions of the tumor where the tumor contacts the surrounding normal tissues. The claimed invention inhibits tumor growth and invasion by blocking activity of matriptase molecules that are shed from tumor cells as well as matriptase molecules that are bound to the surfaces of tumor cells at the tumor periphery. Because the claimed method operates to inhibit tumor invasiveness, growth, and angiogenesis by blocking activity of matriptase enzyme in the peripheral regions of a tumor, the difficult and unpredictable aspects of cytotoxic therapies that require contacting cells in the interior of a solid tumor with a tumor-killing agent as discussed by Jain (1994) and Curti (1993), are not associated with the claimed method of the present invention.

The claimed method of the present invention is also not subject to the difficult and unpredictable aspects of cytotoxic therapies discussed by Hartwell (1997) and White et al. (2001). The non-specific binding of a matriptase inhibitor to matriptase at a non-tumor site is unlikely to result in the death of normal, non-tumor cells; whereas non-specific targeting of a patient's non-cancerous cells by a cytotoxic agent as discussed in Hartwell (1997) may cause serious, life-threatening side effects such as hematologic toxicity. Moreover, the presence of matriptase in non-tumor tissues is not a serious impediment to successful practice of the claimed method, as one of skill in the art would be able to determine the dosage of inhibitor that effectively inhibits matriptase at the site of the targeted tumor without undue experimentation. Unlike the cytotoxic therapies discussed by White et al. (2001), wherein the cytotoxic agent must

bind to an antigen attached to the surface of the targeted tumor cell and is inhibited by soluble antigen, the claimed method operates effectively whether the matriptase that is inhibited is attached to a tumor cell or is a soluble molecule in the extracellular space at the site of the tumor.

As discussed above, one of skill in the art would be able to follow the teachings of the specification and perform the claimed methods comprising assaying to detect matriptase in a biological sample, and administering an agent that blocks the activity of active matriptase and provides therapeutic benefit, without having perform undue experimentation. Withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, for lack of enablement is therefore respectfully requested.

35 U.S.C. §112, first paragraph/written description

Claims 34-36 and 48-49 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description in the specification *See* part 6 of the official action (pages 13-15). The examiner alleges that the application provides descriptive support for a detectable agents that recognizes and binds to matriptase which is an antibody, but fails to provide adequate description for other types of detectable agents.

The applicants respectfully disagree with the examiner, and contend that one of skill in the art would have been able to obtain a detectable agents that recognize and bind to matriptase other than antibodies which are suitable for the invention without undue experimentation. For example, Foltz et al. (2005, abstract attached) describes a non-antibody detectable agent that recognizes and binds to matriptase which is suitable for use in the claimed invention. Nonetheless, in order to expedite prosecution, and without prejudice to the applicants' pursuit of claims that refer to a non-antibody detectable agent in a continuation application, the present claims are amended to specify a detectable agent that recognizes and binds to matriptase which is an antibody. Withdrawal of the rejection under 35 U.S.C. §112, first paragraph, with respect to written description in support of claims 34-36 and 48-49 is respectfully requested.

Claim 41 is rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description in the specification because it is unclear from the specification that antibody M69 is known and readily available to the public or obtainable by a reproducible method described in the specification. *See* part 7 of the official action (pages 16-18).

As stated in the new paragraph added by amendment, hybridomas M69 and M123, which produce antibodies M69 and M123, respectively, were deposited on September 28, 2005, with the American Type Culture Collection (ATCC), currently located at 10801 University Boulevard, Manassas, VA 20110-2209, under the provisions of the Budapest Treaty. Submitted herewith is a Declaration of Biological Deposit in Compliance with the Budapest Treaty, executed by the undersigned attorney of record, which states that the above-described deposits have been made under the terms of the Budapest Treaty, and that all restrictions on the availability to the public of the cell lines so deposited will be irrevocably removed upon the granting of the patent. Accordingly, withdrawal of the rejection of claim 41 under 35 U.S.C. §112, First Paragraph, for lack of written description is respectfully requested.

35 U.S.C. §112, first paragraph/scope

Upon overcoming the above-discussed rejection for lack of enablement, claims 34, 36, 38-44, and 48-49 would remain rejected under 35 U.S.C. §112, first paragraph, because the specification is considered to provide enablement for the claimed method wherein the cancer is an epithelial malignant cancer, but is not considered to be enabling for other types of malignant cancer. *See* part 5 of the official action (pages 11-12).

The applicants respectfully submit that the specification enables one of skill in the art to practice the claimed invention successfully with any type of malignant cancer that expresses matriptase. The application describes assay methods that can be used successfully to detect matriptase in any tumor sample, regardless of type. Using such methods, the applicants have analyzed samples of various types of malignant tumor in a "preliminary screening" and have shown that significant levels of matriptase can consistently be detected in tumor samples of epithelial origin (*e.g., see* paragraph 60). From these results, one of skill in the art would reasonably conclude that malignant tumors of epithelial origin are likely to produce significant levels of matriptase. In addition, analysis of several sarcomas and ovarian tumors of non-epithelial origin did not result in detection of significant levels of matriptase in (*see* paragraphs 56 and 59). Given the relatively small number of malignant tumors of non-epithelial origin that were tested, one of skill in the art would not reasonably conclude from the disclosed data that non-epithelial tumors do not produce matriptase. In view of the well-known genetic and

phenotypic heterogeneity of cancers, such a conclusion could only be drawn after analyzing a wide range of different types of cancer. Moreover, the specification teaches that cells of non-epithelial origin, *i.e.*, granulocytes (leukocytes) and smooth muscle cells, also produce significant amounts of matriptase (*e.g.*, see Figs. 18 and 19), which demonstrates that expression of matriptase is not developmentally limited to cells of epithelial origin. In view of the role of matriptase in promoting tumor invasion and growth, one of skill in the art would therefore reasonably expect that malignant cancers of non-epithelial origin also express matriptase. Indeed, Foltz et al. (2005, abstract attached) have reported that three B cell lymphoma cell lines express matriptase, and have shown that growth of B cell lymphoma tumors produced by transplanting such (Ramos) lymphoma cells into SCID mice can be inhibited by administration of an inhibitory anti-matriptase antibody, as discussed above.

In view of the foregoing, one of ordinary skill in the art would be able to follow the teachings of the specification and perform the claimed method successfully to determine if matriptase is present in any malignant tumor sample, without having to perform undue experimentation. Withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is therefore respectfully requested.

Upon overcoming the above-discussed rejections under 35 U.S.C. §112, first paragraph, claims 34-36, 38, 42-44, and 48-49 would also remain rejected under 35 U.S.C. §112, first paragraph, because the specification is considered to enable the claimed method for treating a malignant cancer with an antibody that binds to activated but not to inactive matriptase and blocks the activity of active matriptase; however, the examiner alleges that it is uncertain whether anti-matriptase antibodies that do not selectively bind to active matriptase would operate effectively. *See* part 8 of the official action (pages 18-19).

The applicants respectfully submit that one of skill in the art at the time of filing would be able to perform the claimed method successfully using either antibody or non-antibody inhibitors of matriptase, without having to perform undue experimentation. At the time of filing, many serine proteases were recognized as targets for therapeutic intervention, and one of skill in the art would have been familiar with reliable, routinely performed methods for obtaining inhibitors of a selected serine protease capable of effectively inhibiting the serine protease *in*

vivo. For example, *see* Katz et al. (1998) and Janc et al. (2000). As discussed above, non-antibody agents capable of blocking the activity of active matriptase were described prior to the filing of the present application (*see* Long et al. (2001) and Enyedy et al. (2001), abstracts attached). The ability of persons of skill in the art to obtain non-antibody inhibitors of matriptase suitable for practicing the claimed invention is also demonstrated by reports describing a variety of such inhibitors that were published after the present application was filed. As noted above, Yamasaki et al. (2003) describe short (3-residue) peptide-based inhibitors of matriptase; Stoop et al. (2003) describe longer peptides (about 20 residues) that inhibit matriptase; Galkin et al. (2004) describe a small-molecule inhibitor of matriptase; Forbs et al. (2005) describe two 3-amidinophenylalanine-type inhibitors of matriptase; and Desilets et al. (2006) describe variants of the serine protease inhibitor eglin c that inhibit matriptase (abstracts attached). The specification, in combination with the knowledge of one of skill in the art at the time of filing, method enables one of skill in the art to perform the claimed method for treating a malignant cancer with an agent that inhibits active matriptase other that an antibody that binds to activated matriptase but not to inactive matriptase. Withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is therefore respectfully requested.

IV. IN CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

Date: June 5, 2006

By_____

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